Introduction. We use clinical, ECG, and biochemical data to stratify risk in patients with chest pain without ST segment elevation. However, the prognostic performance of these studies in relation to time from onset of symptoms is unknown.

Patients and method. In a single-center, prospective study, 321 consecutive patients who had been admitted in the emergency room with a suspected acute coronary syndrome without ST segment elevation were included in the study. Blood samples were collected for CK, CK-MB mass, myoglobin, and cardiac troponin T analysis 6, 12 and 18 hours after the onset of pain and other clinical and ECG data were recorded. Univariate and multivariate analysis was used to identify independent prognostic predictors 6 and 12 hours after the onset of chest pain.

Results. Five variables were independent predictors of the recurrence of ischemia. The model correctly classified 82% of the patients. Age, history of coronary artery disease, prolonged chest pain at rest in the preceding 15 days, pain, ST-segment changes with pain, and cardiac troponin T in excess of 0.1 ng/m 12 hours after the onset of chest pain were identified by logistic regression. A similar model was analyzed at 6 hours, after changing the cutoff point for cardiac troponin T. Cardiac troponin T was considered positive with values of 0.04 ng/ml 6 hours after the onset of chest pain.

Conclusions. More than 80% of the patients admitted to the emergency room with chest pain without ST segment elevation can be correctly classified for new ischemic recurrences using clinical, ECG, and biochemical parameters 6 hours after the onset of pain.

Key words: Unstable angina. Prognosis. Troponin.

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Estratificación de riesgo en pacientes con dolor torácico sin ascenso persistente del segmento ST basado en variables clínicas, ECG y bioquímicas. ¿Cuánto tiempo debemos esperar?

Introducción. Utilizamos datos clínicos, ECG y bioquímicos en la estratificación pronóstica inicial de los pacientes con dolor torácico sin ascenso persistente del segmento ST. Su rendimiento pronóstico global, basado en el tiempo desde el inicio de los síntomas, no ha sido estudiado.

Pacientes y método. Estudio unicéntrico y prospectivo de 321 pacientes consecutivos que acudieron a urgencias con sospecha de síndrome coronario agudo sin ascenso persistente del segmento ST y menos de 12 h de evolución. Se determinaron la creatin cinasa (CK), la CK-MB masa, la mioglobina y la troponina T cardiaca a las 6, 12 y 18 h desde el inicio del cuadro. Analizamos de manera univariada y multivariada las variables clínicas, ECG y bioquímicas para identificar predictores pronósticos independientes a las 6 y 12 h, valorando el rendimiento pronóstico global.

Resultados. En el análisis de regresión logística, 5 variables obtenidas resultaron predictoras independientes para nuevos acontecimientos cardiovasculares y permitieron clasificar correctamente al 82% de los pacientes: edad, cardiopatía isquémica previa, dolor prolongado en los 15 días previos, dolor y cambios del segmento ST con dolor y troponina T superior a 0,1 ng/ml a las 12 h del inicio del dolor. La troponina T, considerada positiva con valores superiores a 0,04 ng/ml a las 6 h, permite un modelo a las 6 h similar al de las 12 h.

Conclusión. Es posible identificar correctamente la evolución clínica de más del 80% de los pacientes que ingresan con dolor torácico sin ascenso del segmento ST con variables clínicas, ECG y bioquímicas en el plazo de 6 h desde el inicio del cuadro.

Palabras clave: Angina inestable. Pronóstico. Troponina.
INTRODUCTION

Patients who go to the emergency room with chest pain without persistent ST segment elevation are a common problem, and are difficult to manage on many occasions. Given the limitations of the initial evaluation, the majority of these patients are admitted to the emergency medicine department, although many of them, in the end, either have a non-cardiac cause for their chest pain or their course is without major complications, so that they could be managed on an outpatient basis. Recognition of these limitations involves the investigation of new techniques and protocols with the aim of achieving greater diagnostic efficacy, understood as those practices that increase sensitivity and specificity without increasing cost and the resulting inconvenience.

There are at present an impressive number of biochemical tests for evaluating the presence of minimal cardiac damage. Nevertheless, these tests have been validated in patients with chest pain with ST segment elevation, evaluating their enzymatic kinetics in this model. On the other hand, the moment at which the pain begins has not been taken into consideration, but rather the moment at which the patient is admitted to the emergency room, so that the concentration ratio of marker to time of the pain is necessarily heterogeneous.

The aim of our study is to create models at 6 and 12 hours from the initiation of chest pain which will allow us to predict the clinical course of patients admitted in a setting of Class IIIB prolonged unstable angina (more than 20 minutes in duration), versus non-Q-wave acute myocardial infarction of less than 12 hours duration. All patients were evaluated by the cardiology department resident, who established the presumed diagnosis of an acute coronary syndrome without persistent ST segment elevation.

We excluded from the study those patients with:

— Persistent ST segment elevation, with fibrinolysis criteria.
— A non-interpretable ECG with a high suspicion of AMI, for whom the attending physician decided to order urgent coronary angiography.
— Secondary chest angina.
— Documented AMI during the previous 2 weeks.
— Chest pain of more than 12 hours duration.
— Renal insufficiency (creatinine >2 mg/dL).

We obtained samples for cardiac markers (total CK activity, CK-MB activity, CK-MB mass, cardiac troponin T, and myoglobin) at 6 and 12 hours after the initiation of the chest pain that resulted in the admission (an additional sample was obtained at 18 hours for total CK and CK-MB activity). It was decided that a sample would not be collected at the moment of the patient’s admission in order to standardize all the determinations with the initiation of the chest pain. In the same manner, we performed an ECG at the time of admission to the emergency department and evolutive ECGs at 6, 12, and 18 hours after admission.

On admission the patients were classified according to the presence of pain and changes on electrocardiogram, and divided into the 3 following categories:

— Without pain on admission.
— Chest pain without ST segment changes apparent on ECG.

Chest pain with reversible ST segment changes or permanent ST segment decline on ECG (greater than 1 mm at 80 ms from the J point).

All the ECGs were evaluated by at least 2 cardiologists, with the opinion of a third cardiologist being obtained in cases of uncertainty, and evolutive ST segment changes in accordance with the pain were noted in the clinical history.

Maximum normal values of the various markers according to our laboratory were:

— CK<200 U/L.
— CK-MB mass <5 ng/dL.
— Myoglobin <60 ng/dL.
— Troponin T< 0.1 ng/dL.

Determination of CK-MB mass, myoglobin, and cardiac troponin T were performed via immunoanalysis with an Elecsys (CARDIAC T) Roche® analyzer.
CK activity and CK-MB mass was analyzed via enzyme reactions with values measured in U/L. All the samples were analyzed immediately by technicians who had no knowledge of the patients’ clinical data.

The biochemical test results were known by the patient’s attending physician and were interpreted according to their criteria, without performance protocols established with regard to the results.

All patients were monitored for at least the first 12 hours following admission and anti-aggregate, anti-angina, and anti-coagulant therapy was begun, according to the attending physician’s criteria.

Events were considered new if they occurred from the period following admission to the emergency room to discharge or clinical followup evaluation at 15 days:

— Death.
— Ischemic recurrence defined as: a new episode of angina in spite of treatment that required urgent coronary angiography with a view toward revascularization and noted as such; a new AMI defined as CK enzyme elevation following admission or according to ECG findings, and the presence of treated primary ventricular fibrillation.
— The development of heart failure that was not present at the time of admission and that required additional treatment, and so noted in the clinical history.

Statistical analysis

A descriptive analysis was performed of the variables noted at the time of admission, expressed as percentages, means, or averages depending on the distribution of the values.

Univariate analysis was performed of events using the $\chi^2$ test for qualitative variables and the Student $t$ test for continuous variables.

A first logistical regression model was obtained for new events at 12 hours after initiation of chest pain that included clinical, ECG, and biochemical variables, using cut points for the biological markers as indicated by the sensitivity and specificity curves for events of each type.

Later a second prognostic model was created, using only the variables obtained during the first 6 hours following the initiation of symptoms. This involved obtaining the most efficacious diagnostic model possible at 6 hours after the initiation of chest pain and comparing it with the best model obtained at 12 hours following initiation of chest pain.

Using the best model, we created a simple risk scale so that it was easy to determine the decisions made for each individual patient. For this, we assigned a point at each 5-point interval of the risk ratio (RR) for each independent variable. In this way, we created a variable summary that gave a total score for each patient.

The scale created was used as a prognostic tool for analyzing the sensitivity, specificity, and predictive values, assuming the prevalence of complications to be similar to that of our sample.

We obtained the ROC curves, both for biochemical determinations and for the models found, estimating the area below the curve as a parameter of prognostic value.

All models were created by using the forward stepwise technique, including the prognostic variables that are considered to be classically prognostic according to the literature at the time of admission to the emergency ward (age, sex, cardiovascular risk factors, pain and ECG changes, abnormal baseline ECG, evolutionary T-wave changes, previous ischemic cardiopathy or peripheral vascular ischemia, or both, and the presence of prolonged chest pain during the 15 days prior to admission), finally adding the biological markers separately; in other words, a determination was entered for each model. We chose as the final model the variables that were adjusted best, with a smaller confidence interval, and we included the interactions that proved to be significant. We used the SPSS version 9.0 statistical package.

RESULTS

We included in our study 321 consecutive patients who went to the emergency room between March, 1998, and December, 1999 with the suspected diagnosis of prolonged unstable angina or non-Q-wave AMI. A total of 6 patients went to the emergency room more than 6 hours after the pain began, and it was not possible to make an initial determination of enzyme values. Nine percent of patients were discharged from the emergency room and 91% were admitted.

Patient characteristics

Of note is the increased incidence of cardiovascular risk factors among the patients: hypercholesterolemia (50.8%), arterial hypertension (62.9%), smoking (56%), and diabetes (30.5%), as well as a mean advanced age (67.5 years). With regard to patient clinical data at the time of admission, the majority still had pain (64.5%), frequently with the presence of electrocardiographic changes (non-persistent ST segment changes in 56% of patients). On the ECGs performed at 6 and 12 hours following admission the most frequent evolutive change was in the T-wave, with normalization of the ST segment (56% of patients).

Analysis of adverse events

A total of 81 patients (25%) developed complications during admission. Of these, the most frequent complication (74% of patients) was a relapse of chest
Evolutive ECG changes

The number of patients admitted in whom it was not possible to confirm the initial diagnosis of an acute cardiac syndrome reached 26%, with a percentage of complications during admission of 0%. The final management of patients was elective revascularization in 25% of cases (n=80), emergency revascularization in 14.6% of cases (n=47), and medical treatment in 60% (n=192).

Univariate analysis identified age and cardiac frequency at the time of admission as variables related to prognosis (P=.001). Predictors of elevation of biological markers also included having experienced a prolonged episode of chest pain during the 15 days prior to admission (P=.008), evolutive changes on ECG (P=.004), and the presence of pain and ECG changes (P=.001).

ROC curves were carried out for the different biochemical markers in relation to the presence of new events during admission. The cut points that were predetermined by our laboratory for the biological markers, with the exception of determination of the cardiac Tropin T (cTnT) at 6 hours after initiation of chest pain, had an adequate sensitivity/specificity relationship for new events during admission. In the case of troponin, we show the cut point at which the sensitivity and specificity relationship was greater (cTnT at 6 hours greater than 0.04 ng/mL) (Figure 1; Table 2).

Multivariate analysis

A first prognostic model was created with variables collected during the first 12 hours following initiation of chest pain; the variables that proved to be independent predictors were age of more than 70 years (RR=1.61; P=.08), previous ischemic cardiopathy (RR=2.21; P=.01), and the presence of prolonged pain different from that which was the cause of admission during the 15 days prior to admission (RR=2.44; P=.03). The presence of pain and ECG changes were also independent predictors, with the peculiarity that they interacted with the presence of an elevation in the biological markers. Of these, we decided to choose in the final model at 12 hours cardiac troponin R, with a cut point of 0.1 ng/mL, because this provided better adjustment of the model (P=.0001), with a better relative risk (RR=30.79), and a smaller RR confidence interval than the rest of the biochemical determinations. The prediction ROC curve for events reached 81.5% of the total in this model (Figure 2).

It must be pointed out that the interaction between the elevation of troponin T levels and the presence or absence of pain and ECG changes was highly significant (P=.008). The significance of this interaction indicated that the risk of the variable of pain and ECG changes varied significantly according to whether or not the cardiac troponin T levels were

<table>
<thead>
<tr>
<th>TABLE 1. Baseline patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Dyslipemia</td>
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<tr>
<td>AHT</td>
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<tr>
<td>Prior ischemic cardiopathy</td>
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<tr>
<td>Familial ischemic cardiopathy</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>Pain and ST segment changes on admission</td>
</tr>
<tr>
<td>Evolutive ECG changes</td>
</tr>
<tr>
<td>S E VPP VPN ROC area</td>
</tr>
<tr>
<td>N=321 (%)</td>
</tr>
<tr>
<td>Ng/mL</td>
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<tr>
<td>Myo (60) 12 h</td>
</tr>
<tr>
<td>Myo (60) 12 h</td>
</tr>
<tr>
<td>CK (200 U/mL) 6 h</td>
</tr>
<tr>
<td>CK (200 U/mL) 12 h</td>
</tr>
<tr>
<td>cTnT (0.04) 6 h</td>
</tr>
<tr>
<td>cTnT (0.1) 6 h</td>
</tr>
<tr>
<td>cTnT (0.1) 12 h</td>
</tr>
<tr>
<td>CK-MBr (5) 6 h</td>
</tr>
<tr>
<td>CK-MBr (5) 12 h</td>
</tr>
<tr>
<td>Myo indicates myoglobin; cTnT, cardiac troponin T.</td>
</tr>
</tbody>
</table>
The univariate ROC curve indicated that troponin T at 12 hours after the initiation of pain had a sensitivity-specificity ratio very similar to that obtained at 6 hours, so that by changing the cut point it was possible to obtain the same sensitivity and specificity at 6 hours and at 12 hours (Figure 1).

A second prognostic model was generated, using only those variables present 6 hours after the initiation of pain, using the optimum cTnT cut point of 0.04 ng/ml, obtaining a model very similar to that at 12 hours, with an ROC curve for the prediction of events that reached 81.1% of the total.

The variables at 6 hours could be summarized, as a function of their prognostic importance for new events, in a scale such as that shown in Table 4. The ROC curve was calculated using a single variable in the model, the scoring on the scale, with a total area under the curve of 79%, providing information very similar to that of the model it was part.

Assuming a prevalence of events in the study population similar to ours (25%), we were able to assume that the risk scale we created, with different sensitivity, specificity, and positive predictive values for each cut point that we chose (Figure 3) was useful diagnos-

### Table 3. Prognostic value at 12 hours after the initiation of chest pain for new events

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnT greater than 0.1 ng/ml (12 h)</td>
<td>30.79</td>
<td>.001</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>1.61</td>
<td>.08</td>
</tr>
<tr>
<td>Previous ischemic cardiopathy</td>
<td>2.21</td>
<td>.01</td>
</tr>
<tr>
<td>Previous prolonged pain</td>
<td>2.44</td>
<td>.03</td>
</tr>
<tr>
<td>Pain without ST segment changes</td>
<td>7.86</td>
<td>.001</td>
</tr>
<tr>
<td>Pain with ST segment changes</td>
<td>46.94</td>
<td></td>
</tr>
<tr>
<td>cTnT&gt;0.1 ng/ml (12 h)+pain without ST segment changes</td>
<td>99.13</td>
<td>.001</td>
</tr>
<tr>
<td>cTnT&gt;0.1 ng/ml (12 h)+pain with ST changes</td>
<td>58.70</td>
<td></td>
</tr>
</tbody>
</table>
tic test.

**DISCUSSION**

**Description of the multivariate model**

The prognostic value at 12 hours reached 82% of patients with some basic tests that included an ECG at the time of admission, enzyme determination of troponin T levels at 12 hours after the initiation of pain, and 3 simple data from the clinical history, such as age, the presence of a prolonged episode of chest pain 15 days prior to admission, and a history of ischemic cardiomyopathy.

The interaction between the variable of pain and ECG changes with the presence of changes in troponins turned out to be clinically and statistically significant. The elevation of troponin levels in patients who already had ECG changes at the time of admission with pain (risk difference=28) did not entail an increase in risk as high as those patients who were admitted with pain and without ECG changes but with a positive troponin determination (risk difference=68) (Table 3). This observation is similar to that of other studies, in which it was concluded that, in patients with ST segment changes, cTnT does not provide an independent predictive value.

On the other hand, the absence of ECG changes on admission did not always apply to low-risk patients and, depending on the troponin T value, these varied from having an excellent to a poor prognosis (percentage of events in patients with pain without ECG changes and without troponin elevation [9%] versus the percentage of events in patients with pain, without ECG changes and troponin T elevation [53%]). DeFilippi et al. prospectively evaluated a series of patients with cTnT elevation and ECG without data indicative of ischemia, and they concluded that in patients with elevated biochemical markers the prevalence of multi-vessel disease and the long-term prognosis were much worse, defining in a population that was an *a priori* low-risk subgroup of patients at very high risk.

The inclusion of prolonged chest pain during the 15 days prior to admission departs from the hypothesis that patients who present at admission with elevated troponin T with normal CK could constitute a subgroup of patients with AMI during the days prior to admission and who went to the emergency room with post-AMI angina that resulted in their admission. Since the kinetics of troponin T are different from those of CKm, these patients were able to maintain elevated cTnT for a longer time than CKm, and it was this discrepancy they presented in these enzymes at the time of admission. In our study, these patients...
had a worse prognosis, with both univariate and multivariate analysis. Nevertheless, we were not able to show that this factor correlates with a greater percentage of patients with elevated troponin and normal CKm. We did not extract our samples at the time of admission, but adjusted them to be taken at 6 and 12 hours following the initiation of chest pain, so that at 6 hours it is likely that the patients could have had elevated CKm from the pain which resulted in their admission.

Galvani\textsuperscript{9} provided data on troponin I and CKm, and found that a third of patients presented with greater concentrations of cTnTI at the time of admission than in the hours following, supporting the hypothesis that an important part of the discrepancy between CKm and troponin T levels in the initial samples can be explained by a recent prior infarct.

**Relationship with previous studies**

Hamm,\textsuperscript{10} using a methodology similar to ours, performed a logistical regression analysis for new events during the first hours of chest pain, but did not find either the ECG or the clinical variables to be significant. Only the presence or absence of troponin at the time of admission (it was guaranteed that at least a sample was taken at 6 hours after initiation of the pain) was seen to have independent prognostic value. We believe our study reflects a greater measure of clinical reality, with the ECG and troponin values, and the interaction between both, having very important prognostic power. In our sample, 20.1\% of the events occurred in patients with negative troponin T at 12 hours following initiation of chest pain, so that this isolated data should not justify the patient’s discharge. The initial ECG is a variable that cannot be ignored despite the level of relevancy that biological markers may reach;\textsuperscript{7,11} this is shown by the analysis of events in our sample, with a risk 2 times higher in those patients who present with ECG changes associated with pain than in those patients in whom the pain does not cause ECG changes. Hamm reported in his series a 1.1\% incidence rate for complications in patients with a negative troponin T determination at 6 hours following admission. Nevertheless, these results call for prudence in the case of patients who present with an ST segment decline on admission, because in these patients, in spite of an elevation of troponin T not being present, the incidence rate for complications reached 2.8\%, and the mortality rate reached 20\% at 30 days in patients with negative troponin T.\textsuperscript{12}

The risk scale we created is very similar to that obtained from the TIMI study,\textsuperscript{13} which analyzed some final parameters similar to ours in a cohort of 3910 patients who were admitted with prolonged unstable angina versus non-Q-wave AMI. Nevertheless, the interaction between a positive troponin determination and the presence of ECG changes is not reflected, and the presence of prolonged pain during the 15 days prior to admission is also not included in their risk evaluation. On the other hand, taking aspirin during the previous week and the presence of 2 or more episodes of chest pain during the 24 hours prior to admission as risk factors for complications were not studied in our patient sample.

**Implications for a chest pain unit**

A chest pain unit should have a risk stratification system in place that is above all highly sensitive, with an elevated negative predictive value so that patients susceptible to developing potentially serious complications are not discharged.\textsuperscript{14,15} On the other hand, it should be capable of detecting patients with a high probability of developing complications so that they can be referred to units with specialized personnel and the availability of emergency revascularization procedures. The intermediate-risk group of patients could be admitted to the floor for observation and prognostic stratification.

Risk stratification must be carried out in as little time as possible in order to decrease stays in the emergency room and the time taken to make decisions. The new cut point for troponin T offers the same returns in the 6 hour model as in the 12 hour model, permitting a decrease in waiting time. The great myocardial specificity of cardiac troponin T,\textsuperscript{2} the absence of detectable levels in plasma in normal individuals,\textsuperscript{2} and the controlled extraction of samples according to the amount of time elapsed from the initiation of chest pain explains why minimal elevations of this marker have prognostic connotations.\textsuperscript{16}

The creation of a simple scale at 6 hours allows us to classify the patient population according the risk of developing new ischemic events during admission. According to Figure 3, a score of 3 or less is associated with a probability of developing new episodes of less than 3\%. In our sample, 34.6\% of the population presented with this low-risk profile, so that the patients could be managed on an outpatient basis.

Patients with an elevated incidence rate of episodes would benefit from more intensive attention, with access to new anti-aggregate therapies and revascularization. According to the model created, 40\% of patients had an incidence rate of new ischemic episodes of greater than 40\% (a score higher than 10). The patients with an intermediate risk level (a score higher than 3 and lower than 11) could be treated on the ward, reaching 25\% of the population, with a risk for new episodes of between 3.8\% and 21\%.

**Study limitations**

This was an observational study, with biochemical
data being non-blinded for the attending physicians. Although specific action protocols do not exist with respect to biological markers, it was not considered ethical to blind the results of the biochemical tests, so a bias may exist with regard to the classification of events as a function of the biochemical tests. The greater majority of events involved refractory angina and required, for their classification, that note was made of their urgent character. We did not consider the performance of a non-emergency revascularization to be an event.

The patient population was selected by cardiologists, who estimated if the chest pain was sufficiently suggestive of ischemia, whether due to clinical data, an ECG, or the patient’s history, to carry out followup at 12 hours with continuous monitoring. This parameter resulted in our sample being homogeneous, with a high incidence of episodes. The predictive values of the models created have to be adjusted for the prevalence of episodes in the patient sample analyzed. A selection of low-risk patients would present, for this same model, higher negative predictive values and lower positive predictive values, by increasing the incidence of false positives.

Ninety-one percent of patients were admitted so that, although we were able to select a posteriori 30% of the patients with a low-risk profile, it must be taken into account that the treatment and course of these patients evolved inside a hospital. Patients with a low-risk profile could be discharged following an initial evaluation, once they were able to complete the treatment parameters and follow the lifestyle established by the hospital, and being re-evaluated as outpatients in a timely manner.

Although the models described present data that has internal validity, their external validity must be confirmed by a new sample of patients with similar inclusion criteria in order to be able to generalize their use.

Thus, we conclude that the initial prognostic evaluation of a patient with chest pain suggestive of ischemia can be completed within a period of 6 hours after the initiation of the chest pain, if we change the positivity limit for cTnT to 0.04 ng/mL. When using the 0.1 ng/mL limit, we should wait 12 hours. This evaluation includes clinical variables, ECG, and biochemical values and predicts the presence or absence of events in more than 80% of patients, so that it can be used as a summary diagnostic test.

REFERENCES